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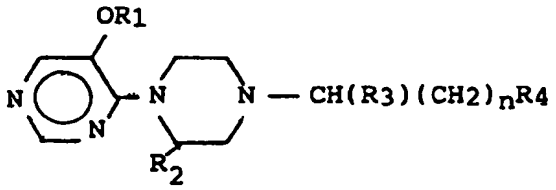

(I)

(57) Abstract

Pyrimidinyl piperazine derivatives of formula (I), wherein R_1, R_2 and R_3 are independently H or C_1-C_4-alkyl; R_4 is optionally substituted phenyl; and n is 1 to 5; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

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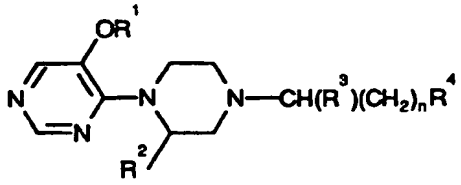
Pyrimidinyl-piperazine derivatives and their use as medicaments

The present invention relates to pyrimidinyl piperazine derivatives, processes and intermediates useful in their preparation, pharmaceutical compositions containing them and their use in therapy in particular for the treatment and/or prophylaxis of disorders characterised by excessive vasodilatation such as migraine.

EP-A-464558 discloses certain indolylalkylpyrimidinyl piperazine derivatives useful in the treatment of vascular headaches of the migraine type.

The present invention provides, in a first aspect, a compound of structure (I) :



Structure (I)

wherein :

R^1, R^2 and R^3 are independently hydrogen or C_{1-4}alkyl;

R^4 is optionally substituted phenyl; and

n is 1 to 5; or

a pharmaceutically acceptable salt, solvate or hydrate thereof.

Preferably R^1 is C_{1-4}alkyl.

Preferably R^2 is H.

Preferably R^3 is H.

Suitably R^4 is unsubstituted phenyl or phenyl substituted by 1 to 3 groups selected from halo, C_{1-4}alkyl, C_{1-4}alkoxy, $-CO_2R^5$, $-NHCOR^5$, $-(CH_2)_mCONR^6R^7$, $-(CH_2)_mSO_2NR^6R^7$, $-(CH_2)_mNHSO_2R^8$, NO_2, $-NR^6R^7$, CN, CF_3, or CF_3O, wherein R^5 to R^7 are independently hydrogen or C_{1-4}alkyl, R^8 is C_{1-4}alkyl and m is O or 1.

Suitably n is 2 to 4, preferably n is 2.

Examples of C_{1-4}alkyl groups (alone or as part of another group, e.g. C_{1-4}alkoxy) include methyl, ethyl, propyl or butyl which can be straight chain or branched.

Examples of halo groups include fluoro, bromo, chloro and iodo.

Particular compounds of structure (I) include :

4-(5-methoxy-4-pyrimidinyl)-1-[3-(phenyl)propyl]piperazine,

4-(5-methoxy-4-pyrimidinyl)-1-(4-phenylbutyl)piperazine,

4-(5-methoxy-4-pyrimidinyl)-1-[4-(4-nitrophenyl)butyl]piperazine,

4-(5-methoxy-4-pyrimidinyl)-1-[4-(4-aminophenyl)butyl]piperazine, and

4-(5-methoxy-4-pyrimidinyl)-1-[4-(4-acetylaminophenyl)butyl]piperazine,

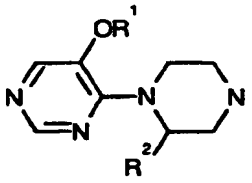
and pharmaceutically acceptable salts, solvates and hydrates thereof.

Pharmaceutically acceptable acid addition salts of the compounds of structure (I) include, for example, those formed with inorganic acids e.g. hydrochloric, sulphuric, methane sulphonic or phosphoric acids and organic acids e.g. succinic, maleic, acetic or fumaric acid. Other non-pharmaceutically acceptable salts e.g. oxalates may be used for example in the isolation of compounds of formula (I), and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

It will be appreciated that certain compounds of structure (I) for example where R^3 is other than hydrogen may contain an assymetric centre. Such compounds will exist as two (or more) optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two, are included within the scope of the present invention. Further, all diastereomeric forms possible (pure enantiomers and mixtures thereof) are within the scope of the invention.

In a further aspect the present invention provides a process for preparing a compound of structure (I) or a salt, solvate or hydrate thereof which comprises :

(a) reaction of a compound of structure (II) :



Structure (II)

wherein R^1 and R^2 are as hereinbefore defined with a compound of structure (III) :

$$L^1CH(R^3)(CH_2)_nR^4$$

Structure (III)

wherein L^1 is a leaving group and R^3, R^4 and n are as hereinbefore defined; or

(b) reaction under reductive amination conditions of a compound of structure (II) as hereinbefore defined with a compound of structure (IV) :

$$R^3C(O)(CH_2)_nR^4$$

Structure (IV)

wherein R^3, R^4 and n are as hereinbefore defined;

and thereafter optionally :

- converting one R^4 group to another R^4 group;
- forming a pharmaceutically acceptable salt, solvate, or hydrate thereof.

The reaction of a compound of structure (II) with a compound of structure (III) is suitably performed in an organic solvent such as acetonitrile at ambient or elevated

temperature e.g. 30-50°C, conveniently at the reflux temperature of the reaction mixture. Examples of L^1 include halo, such as chloro, bromo or iodo, tosyl or mesyl. Optionally a phase transfer catalyst such as tetrabutylammonium hydrogen sulphate or tetrabutylaammonium iodide may be added.

Suitable reductive amination conditions for the reaction of a compound of structure (II) with a compound of structure (IV) include catalytic hydrogenation or reaction in the presence of a suitable reducing agent, such as sodium cyanoborohydride or sodium borohydride. The reaction is suitably performed in an organic solvent such as methanol or ethanol at ambient or elevated temperature preferably at ambient temperature.

Compounds of structure (II) are known from EP-A-464558.

Standard functional group interconversions can be used to convert one R^4 group to another R^4 group. For example a compound of structure (I) wherein R^4 is an aminophenyl group can be converted to a R^5CONH-phenyl group by reaction with a suitable acylating agent, for example acetic anhydride when R^5 is methyl.

Compounds of structures (III) and (IV) can be prepared by standard procedures involving the introduction and manipulation of substituents around a benzene ring.

Acid addition salts of compounds of structure (I) can be prepared by standard procedures, for example, by reaction with suitable organic and inorganic acids, the nature of which will be apparent to persons skilled in the art.

Compound of structure (I) have been found to be agonists at 5-HT_1-like receptors and are expected to have utility in medicine in the treatment and/or prophylaxis of migraine, and other conditions associated with cephalic pain, such as cluster headache and headache associated with vascular disorders and other neuralgia.

In a further aspect the present invention provides compounds of structure (I) for use as medicaments and their use in the manufacture of medicaments for treating conditions where a 5-HT_1-like receptor agonist is indicated, in particular migraine.

In a further aspect, the present invention provides a method of treating conditions where a 5-HT_1-like receptor agonist is indicated, in particular migraine which comprises administering to a subject in need thereof an effective amount of a compound of structure (I) or a pharmaceutically acceptable salt, solvate or hydrate thereof.

For use in medicine, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of structure (I) or a pharmaceutically acceptable salt, solvate or hydrate thereof and a pharmaceutically acceptable carrier.

The compounds of the invention may be administered by any convenient route, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluoro-chlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The pharmaceutically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 10 mg and 400 mg e.g. between 10 mg and 250 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg e.g. between 1 mg and 25 mg, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

BIOLOGICAL DATA

RABBIT BASILAR ARTERY

Experiments were performed in intracranial arteries from rabbit isolated basilar artery in a similar method to one described previously (Parsons and Whalley, 1989. Eur J Pharmacol 174, 189-196.).

In brief, rabbits were killed by overdose with anaesthetic (sodium pentobarbitone). The whole brain was quickly removed and immersed in ice cold modified Kreb's solution and the basilar artery removed with the aid of a dissecting microscope. The Krebs solution was of the following composition (mM) Na^+ (120); K^+ (5); Ca^{2+} (2.25); Mg^{2+} (0.5); Cl^- (98.5); SO_4^{2-} (1); EDTA (0.04), equilibrated with 95% O_2/5% CO_2. The endothelium was removed by a gentle rubbing of the lumen with a fine metal wire. Arteries were then cut into ring segments (ca 4-5 mm wide) and set up for recording of isometric tension in 50 ml tissue baths in modified Krebs solution with the additional supplement of (mM); Na^{2+} (20); fumarate (10); pyruvate (5); L-glutamate (5) and glucose (10). The arteries were then placed under a resting force of 3-4 mN maintained at 37°C and the solution bubbled with 95% O_2/5% CO_2.

After tests for initial reactivity with 90 mM KCl depolarising solution and for lack of acetylcholine-induced relaxation of 5-HT (10 mM) precontraction, cumulative concentration-effect curves (2 nM-60 mM) to 5-HT were constructed in the presence of ascorbate 200 mM, cocaine 6 mM, indomethacin 2.8 mM, ketanserin 1 mM and prazosin 1 mM.

Following a 45-60 min wash period, cumulative concentration-effect curves to the test compounds or 5-HT (as a time match control) were constructed in the presence of ascorbate, indomethacin, cocaine, ketanserin and prazosin.

Example 1

4-(5-Methoxy-4-pyrimidinyl)-1-[3-(phenyl)propyl]piperazine (oxalate salt)

To a solution of 1-(5-methoxy-4-pyrimidinyl)piperazine (0.28g) prepared according to the method of EP 0464558-A1 in acetonitrile (15ml) containing tetrabutylammonium iodide (0.027g) and potassium carbonate (0.22g), 3-phenyl-1-(4-toluenesulphonyloxy)propane (0.42g) was added and the mixture boiled for 150 minutes. The mixture was filtered, the residue washed with methanol, filtrates combined and solvent removed at reduced pressure. The residue was dissolved in dichloromethane washed with water, dried (K_2CO_3) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 0-3% methanol/dichloromethane eluant) to give after combining appropriate fractions the title compound (0.23g) m.p. >175°C (decomp) after conversion to the oxalate salt and recrystallisation from methanol/diethyl ether.

^{1}H NMR (d_6-dmso) 1.95(m,2H), 2.62(t,2H), 2.96(t,2H), 3.16(m,4H), 3.86(s,3H), 3.87(m,4H), 7.18-7.33(m,5H), 8.13(s,1H) and 8.31(s,1H).

Example 2

4-(5-Methoxy-4-pyrimidinyl)-1-(4-phenylbutyl)piperazine (oxalate salt)

From 1-(5-methoxy-4-pyrimidinyl)piperazine (0.27g) and 4-phenyl-1-(4-toluenesulphonyloxy)butane (0.42g) the title compound (0.14g) m.p. >205°C (decomp) was prepard according to the method of Example 1.
^{1}H NMR ($d_6$dmso) 1.61(m,4H), 2.61(t,2H), 3.01(t,2H), 3.18(m,4H), 3.87(s,3H), water peak masking 4H, 7.17-7.32(m,5H), 8.15(s,1H) and 8.32(s,1H).

Example 3

4-(5-methoxy-4-pyrimidinyl)-1-[4-(4-nitrophenyl)butyl]piperazine (oxalate salt)

From 1-(5-methoxy-4-pyrimidinyl)piperazine (10.8g) and 4-(4-nitrophenyl)-1-(4-toluenesulphonyloxy)butane (6.0g), the title compound (7.31g) isolated as the free base was prepared according to the method of Example 1 but using tetrabutylammonium hydrogen sulphate (0.52g) instead of tetrabutylammonium iodide. From the free base (0.2g) the oxalate salt (0.12g), m.p. 177-180°C after recrystallisation from ethanol, was prepared.

Example 4

4-(5-methoxy-4-pyrimidinyl)-1-[4-(4-aminophenyl)butyl]piperazine (oxalate salt)

A solution of 4-(5-methoxy-4-pyrimidinyl)-1-[4-(4-nitrophenyl)butyl]piperazine (0.81g) in acetic acid (20ml) was diluted with water (20ml) and aqueous titanium trichloride (30%, 3.32g) added. The mixture was stirred for 10 minutes solvent removed at reduced pressure, the residue dissolved in water (20ml) and made basic with 5N sodium hydroxide. Precipitated material was removed by filtration and the filtrate extracted with ethyl acetate (3 x 20ml). The combined organic extracts were combined, dried ($MgSO_4$) and solvent removed to give the free base (0.16g) of the title compound. The free base (0.16g) was converted to the title compound oxalate salt (0.25g) m.p. 145-148°C after recrystallisation from ethanol.

Example 5

4-(5-methoxy-4-pyrimidinyl)-1-[4-(4-acetylaminophenyl)butyl]piperazine oxalate salt

A solution of 4-(5-methoxy-4-pyrimidinyl)-1-[4-(4-aminophenyl)butyl]piperazine (0.08g) in toluene containing triethylamine (0.05g) and acetic anhydride (0.03g) was added at room temperature. The mixture was stirred for 1 hour, solvent removed at reduced pressure and the residue column chromatographed (silica gel, 5% methanol / dichloromethane eluant) to give the free base of the title compound (0.09g). The free 0.09g) was dissolved in ethanol and oxalic acid (0.06g) in ethanol added. The precipitated title compound (0.118g) m.p. 186-188°C was separated by filtration.

Pharmaceutical formulations

Example A

A tablet for oral administration is prepared by combining

	Mg/Tablet
Compound of formula (I)	100
lactose	153
starch	33
crospovidone	12
microcrystalline cellulose	30
magnesium stearate	2
	330 mg

into a 9 mm tablet.

Example B

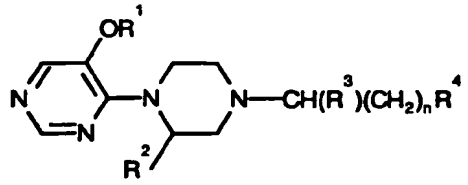
An injection for parenteral administration is prepared from the following

	% w:w
Compound of formula (I)	0,50% (w:v)
1M citric acid	30% (v:v)
sodium hydroxide (qs)	to pH 3.2
water for injection BP	to 100 ml

The compound of formula (I) is dissolved in the citric acid and the pH slowly adjusted to pH 3.2 with the sodium hydroxide solution. The solution is then made up to 100 ml with water, sterilised by filtration and sealed into appropriately sized ampoules and vials.

Claims

1. A compound of structure (I) :



Structure (I)

wherein :
R^1, R^2 and R^3 are independently hydrogen or C_{1-4}alkyl;
R^4 is optionally substituted phenyl; and
n is 1 to 5; or
a pharmaceutically acceptable salt, solvate or hydrate thereof.

2. A compound according to claim 1 wherein R^1 is C_{1-4}alkyl.

3. A compound according to claim 1 or 2 wherein R^2 is H.

4. A compound according to any one of claims 1 to 3 wherein R^3 is H.

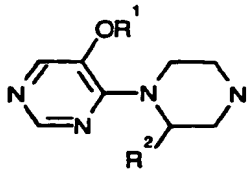
5. A compound according to any one of claims 1 to 4 wherein R^4 is unsubstituted phenyl or phenyl substituted by 1 to 3 groups selected from halo, C_{1-4}alkyl, C_{1-4}alkoxy, $-CO_2R^5$, $-NHCOR^5$, $-(CH_2)_mCONR^6R^7$, $-(CH_2)_mSO_2NR^6R^7$, $-(CH_2)_mNHSO_2R^8$, NO_2, $-NR^6R^7$, CN, CF_3, or CF_3O, wherein R^5 to R^7 are independently hydrogen or C_{1-4}alkyl, R^8 is C_{1-4}alkyl and m is O or 1.

6. A compound according to any one of claims 1 to 5 wherein n is 2 to 4.

7. A compound according to claim 1 selected from :
4-(5-methoxy-4-pyrimidinyl)-1-[3-(phenyl)propyl]piperazine,
4-(5-methoxy-4-pyrimidinyl)-1-(4-phenylbutyl)piperazine,
4-(5-methoxy-4-pyrimidinyl)-1-[4-(4-nitrophenyl)butyl]piperazine,
4-(5-methoxy-4-pyrimidinyl)-1-[4-(4-aminophenyl)butyl]piperazine, or
4-(5-methoxy-4-pyrimidinyl)-1-[4-(4-acetylaminophenyl)butyl]piperazine,
or a pharmaceutically acceptable salt, solvate or hydrate thereof.

8. A process for preparing a compound of structure (I) or a salt, solvate or hydrate thereof which comprises :

(a) reaction of a compound of structure (II) :



Structure (II)

wherein R^1 and R^2 are as defined in claim 1 with a compound of structure (III) :

$$L^1CH(R^3)(CH_2)_nR^4$$

Structure (III)

wherein L^1 is a leaving group and R^3, R^4 and n are as defined in claim 1; or

(b) reaction under reductive amination conditions of a compound of structure (II) as hereinbefore defined with a compound of structure (IV) :

$$R^3C(O)(CH_2)_nR^4$$

Structure (IV)

wherein R^3, R^4 and n are as hereinbefore defined;

and thereafter optionally :

- converting one R^4 group to another R^4 group;
- forming a pharmaceutically acceptable salt, solvate, or hydrate thereof.

9. A compound of structure (I) as defined in claim 1 or a pharmaceutically acceptable salt, solvate or hydrate thereof for use as a medicament.

10. A pharmaceutical composition comprising a compound of structure (I) as defined in claim 1 or a pharmaceutically acceptable salt, solvate or hydrate thereof and a pharmaceutically acceptable carrier.

11. A method of treating a condition where a 5-HT_1-like receptor agonist is indicated, which comprises administering to a subject in need thereof an effective amount of a compound of structure (I) as defined in claim 1 or a pharmaceutically acceptable salt, solvate or hydrate thereof.

INTERNATIONAL SEARCH REPORT

Inte mal Application No
PCT/EP 93/03565

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D239/46 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 464 558 (BRISTOL-MYERS) 8 January 1992 see the whole document	1,8-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
5 April 1994	20. 04. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Francois, J

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte mal Application No
PCT/EP 93/03565

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0464558	08-01-92	AU-B-	643038	04-11-93
		AU-A-	7941691	02-01-92
		CA-A-	2043709	30-12-91
		JP-A-	4230378	19-08-92